REMARKS

Claims 30-48 are pending in the subject application. By this Amendment, applicants have added new Claims 49-99. Applicants maintain that new Claims 49-99 do not introduce new matter into the application. The new claims are supported throughout the specification, and for example by Claims 30-48. Support for mu, delta, and kappa opioid receptor subtypes also may throughout the specification, and for example at page 17, lines 14-16, and at page 20, lines 10-12. Finally, new Claims 60, 61, 63, 65, 67, 69, 87, 88, 90, 92, 94 and 96 are supported throughout the specification, and for example, at page 11, lines 1-3. Accordingly, entry of new claims 44-99 is respectfully requested.

The specification also has been amended to update and correct the continuing data for the subject application. The amendments to the specification do not introduce new matter. Accordingly, entry of the amendments to the specification is respectfully requested.

In view of the remarks which follow, applicants respectfully request that the Examiner reconsider and withdrawal the various rejections set forth in the February 19, 2003 Office Action, and earnestly solicit allowance of Claims 30-99.

Rejection Based on Levine

In the Office Action, the Examiner rejected Claims 30-33, 36, 40-44 and 46 under 35 U.S.C. 102(b) an anticipated by Levine, et al. (J. Clin. Invest., 82: 1574-1577, 1988, "Levine"). Applicants respectfully traverse this rejection.

Levine describes studies evaluating the analgesia produced by pentazocine, morphine and naloxone, in humans and rats. Levine stated that the analgesia produced by pentazocine (60 mg i.v. in humans) was potentiated by low-dose naloxone, while the analgesia produced by morphine was attenuated by low-dose naloxone. Levine, p. 1574, abstract. Levine does not teach the administration of an excitatory opioid receptor antagonist in an amount effective to enhance the analgesic potency of an opioid agonist. In fact, Levine's findings that naloxone attenuates morphine analgesia is a teaching away from the present invention. With respect to Levine's statements concerning pentazocine, pentazocine is known to possess mixed agonist/antagonist properties. Goodman and Gilman (1995) acknowledge that pentazocine has antagonist activity and may precipitate withdrawal symptoms in patients who have been receiving opioids on a regular basis, and high doses of pentazocine (e.g., 60 mg i.v.) are known to induce withdrawal symptoms in opioid addicts. See, Appendix 1, Goodman and Gilman, pp. 276-277. Similarly, 60 mg of pentazocine administered i.v. has been shown to exhibit antagonistic properties in methadone dependent addicts. See, Appendix 2, Strain EC. et al., J. Pharm. Exp. Ther. 267(2): 624-634, 1993. Levine simply does not teach enhancing analgesia of an agonist by the administration of an antagonist. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejections Based on Lewenstein

Claims 30-32 and 36 were rejected under 35 U.S.C. 102(b) as anticipated by Lewenstein, U.S. Patent No. 3,493,657 ("Lewenstein"). Claims 33, 40-44 and 46 also were rejected under 35 U.S.C. 103 as unpatentable over Lewenstein. Applicants respectfully traverse both rejections.

Lewenstein describes a composition including morphine and N-allyl-14-hydroxy-dihydro-nor-morphinone (i.e., naloxone). Lewenstein states that the composition has a "strong analgesic as well as antagonist effect, without the occurrence of undesired or dangerous side effects". Lewenstein, Col. 1, lines 44-50. The "strong analgesic" effect is not a teaching of naloxone enhancing the analgesic potency of morphine. Rather, Lewenstein states that the composition is made by mixing morphine "a very strong analgesic" with naloxone. Lewenstein, Col. 1, lines 44-55. The "antagonist effect" relates to the antagonistic action of naloxone. The "undesired or dangerous side effects" relate to effects of the prior antagonist, nalorphine, which was known to cause side effects such as confusion, dream states or frightening experiences. Lewenstein, Col. 1, lines 19-35. Lewenstein does not teach or suggest the administration of an antagonist in an amount effective to enhance the analgesic potency of an agonist. Accordingly, reconsideration and withdrawal of the rejections based on Lewenstein is respectfully requested.

Rejections Based on Pachter, et al. (U.S. Patent No. 3,879,555)

Claims 30-40 were rejected under 35 U.S.C. 102(b) as anticipated by Pachter, et al., U.S. Patent No. 3,879,555 ("Pachter 1"). Claims 41-48 also were rejected under 35 U.S.C. 103 as unpatentable over Pachter 1. Applicants respectfully traverse both rejections.

Pachter 1 describes an oral composition that includes a combination of an analgesic and an orally inactive dose of naltrexone, that if injected by a drug addict, does not produce analgesia, euphoria or physical dependence, and induces withdrawal symptoms. Pachter 1, Col. 4, lines 1-10; Col. 5, lines 45-52. Pachter 2 also describes

treating a narcotic addict with the oral composition containing both naltrexone and methadone. Pachter 1, Col. 5, lines 15-19. If the oral composition were injected by the addict, then the antagonist would block analgesia and euphoria, and induce withdrawal symptoms. Pachter 1 does not teach the administration of an antagonist in an amount effective to enhance the analgesic potency of an agonist. Rather, Pachter 1 teaches the opposite, namely that the antagonist blocks the analgesia of an agonist. Accordingly, reconsideration and withdrawal of the rejections based on Pachter 1 is respectfully requested.

Rejection Based on Pachter, et al. (U.S. Patent No. 3,773,955)

Claims 30-33, 36 and 38 were rejected under 35 U.S.C. 102(b) as anticipated by Pachter, et al., U.S. Patent No. 3,773,955 ("Pachter 2"). Claims 33, 41-44 and 46 also were rejected under 35 U.S.C. 103 as unpatentable over Pachter 2. Applicants respectfully traverse both rejections.

Pachter 2, like Pachter 1, describes an orally effective analgesic composition that includes a combination of an analgesic and an orally inactive dose of an antagonist, that if injected by a drug addict, does not produce analgesia, euphoria or physical dependence, and induces withdrawal symptoms. Pachter 2, Col. 1, lines 9-21. However, Pachter 2 describes the use of naloxone, while Pachter 1 describes the use of naltrexone. Similar to Pachter 1, Pachter 2 does not teach the administration of an antagonist in an amount effective to enhance the analgesic potency of an agonist. Rather, Pachter 2, like Pachter 1, teaches the opposite, namely that the antagonist blocks the analgesia of an agonist. Accordingly, reconsideration and withdrawal of the rejections based on Pachter 2 is respectfully requested.

35 U.S.C. §112, Second Paragraph Rejection

Claims 32 and 34 (sic 31 and 32) were rejected under 35 U.S.C. 112, second paragraph. In this regard, the Examiner stated that it is unclear if "similarly acting" compares the recited compound species or the activities recited in the independent claims.

In response, applicants note that "similarly acting opioid alkaloids and opioid peptides" refers to opioid alkaloids and opioid peptides that act similar to the specific opioids listed in Claims 31 and 32. Claims 31 and 32 as being dependent upon Claim 30, include the limitations of Claim 30. This language is included in certain claims of predecessor patent family members (U.S. Patent Nos. 5,767,125, 5,580,876, and 5,512,578) and as such was previously determined to clearly define applicants' invention. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Double Patenting Rejection

Claims 30-48 were rejected for obviousness-type double patenting over Claims 1-32 of U.S. Patent No. Re 36,547, Claims 1-31 of U.S. Patent No. 6,362,194, Claims 1-7 of U.S. Patent No. 6,096,756, Claims 1-18 of U.S. Patent No. 5,767,125, and Claims 1-10 of U.S. Patent 5,472,943.

Applicants attach hereto as Appendix 3 terminal disclaimers for U.S. Patent Nos. Re 36,547, 6,362,194, 5,767,125 and 5,472,943. The appropriate fee for recording each terminal disclaimer ($55.00 each) fee is also included with this response. Claims 1-7 of U.S. Patent No. 6,096,756 relate to the treatment of chronic pain with an

excitatory opioid receptor antagonist, while the claims of the current application relate to an agonist and an antagonist. Therefore, applicants believe the Examiner was mistaken in including U.S. Patent No. 6,096,756 in the current rejection. Reconsideration and withdrawal of this rejection is respectfully requested.

Information Disclosure Statement

Applicants filed an Information Disclosure Statement with a Request for Continued Examination on December 6, 2002. Applicants respectfully request that the Examiner initial the Forms PTO/SB08A-B that were submitted with the Information Disclosure Statement to indicate that the references listed on the forms have been considered, and return a copy of the initialed forms to the undersigned.

No fee, other than the $465.00 extension of time fee, the $450.00 additional claim fee, and the $220.00 fee for recording the terminal disclaimers ($55.00 per terminal disclaimer) is deemed required in connection with this response. If any additional fee is required to preserve the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785. Overpayments may also be credited to Deposit Account No. 01-1785.

Respectfully submitted,

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